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How do I interpret …
Candida from abdominal drains?

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Candida from abdominal drains

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How do I interpret *Candida* from abdominal drains

An innocent bystander

Samples obtained from drainage tubes are not valuable except for evaluation of colonization

- *Candida* is a normal flora of the gastrointestinal tract. Similar to *enterococci*, it has remained unclear whether its presence in an intra-abdominal specimen is relevant for therapy or outcome.
- Unlike candidemia, isolation of *candida* in an intra-abdominal specimen is not synonymous with the need for antifungal therapy.
- However, differentiation between colonization and infection is difficult.

Bassetti M, et al. Intensive Care Med. 2013;39:2092; Afzal Azim, et al. EMJ Nephrol. 2017;5:83

How do I interpret *Candida* from abdominal drains

A significant finding

Intra-abdominal infections

- Intra-abdominal infections are common surgical emergencies and have been reported as major contributors to non-trauma deaths in the emergency departments worldwide.

- The cornerstones of effective treatment are
  - early recognition
  - adequate source control
  - appropriate antimicrobial therapy

Source of intra-abdominal infection

4553 patients from 132 hospitals worldwide, 2014-2015

Source of infection	Number (%)
Appendicitis	1553 (34.2)
Cholecystitis	837 (18.5)
Post-operative	387 (8.5)
Colonic non-diverticular perforation	269 (5.9)
Gastro-duodenal perforations	498 (11)
Diverticulitis	234 (5.2)
Small bowel perforation	243 (5.4)
Others	348 (7.7)
PID Pelvic inflammatory disease	50 (1.1)
Post traumatic perforation	114 (2.5)
Total	4553 (100)

Sartelli M, et al. World J Emerg Surg. 2015;10:61

Intra-abdominal candidiasis

- Is the second most common form of invasive candidiasis after candidemia.
- Is estimated that annual 60,000–100,000 cases developed globally.
- Includes intra-abdominal abscess (30-60%), secondary peritonitis after repeated leak (30-40%), infected pancreatic necrosis (5-10%), cholecystitis or cholangitis (5-10%), primary peritonitis (5%).
- Unfortunately, blood cultures have poor sensitivity, as *Candida* is rapidly cleared from the blood.

J Fungi 2017;3:57; *Intensive Care Med* 2013;39:2092; Intensive Care Med. 2015;41:1601; Surgery today 2007;37:207; PLoS One 2016;11: e0153247; Afzal Azim, et al. EMJ Nephrol. 2017;5:83; Clin Infect Dis. 2013;56:1284

Candida in acute pancreatitis

Associated with longer hospital stay and mortality

Candida spp.	True Group I	Possible Group II	
C. albicans	8	7	
C. tropicalis	9	9	
C. glabrata	4	3	
C. krusei	1	—	1
Total	22	19	41

Group I: Patients with a true *Candida* infection of the pancreas; Group II: Patients with a possible *Candida* infection of the pancreas

Severity of pancreatitis
Total parenteral nutrition
Surgical intervention
Sepsis
Fluconazole prophylaxis

41/335 patients with acute pancreatitis (12%)

- **Possible:** Positive drain fluid effluents at least twice, without any *Candida* isolation from pre/per operative samples of pancreas; same *Candida* species isolated from the blood in 9 patients (9/19, 47%).
- **Additional** 19 patients with *Candida* isolated exclusively from the blood

Chakrabarti A, et al. Surgery today 2007; 37: 207

Candida species are not the same

- Polymicrobial intra-abdominal infections (IAIs) are clinically prevalent and cause significant morbidity and mortality, especially those involving fungi.
- This study developed a mouse model of IAI and demonstrated that intraperitoneal inoculation with C. *albicans* or other virulent non-*albicans Candida* species plus *Staphylococcus aureus* resulted in 70-80% mortality in 48 to 72 h due to robust local and systemic inflammation.
- Inoculation with C. *dubliniensis* or C. *glabrata* with *S. aureus* resulted in minimal mortality.

Elizabeth A. Lilly, et al. Immune Protection against Lethal Fungal-Bacterial Intra-Abdominal Infections. mBio. 2018; 9: e01472

Non-Culture-Based Methodologies

- Cultures are negative in ~50% of invasive candidiasis.
- Nonculture tests:
  - mannan/antimannan
  - *Candida albicans* germ tube antibody
  - 1,3-β-D-glucan
  - PCR
  - T2Candida panel

Performance of nonculture tests for diagnosing intra-abdominal candidiasis

Test	Method	Study groups (*n*)	Sensitivity (%)	Specificity (%)
Mannan	Platelia	IAC (20) vs at-risk ICU pts (202)	40	67
Antimannan	Platelia	IAC (20) vs at-risk ICU pts (202)	25	89
C. albicans germ tube antibody	Vircell	IAC (20) vs at-risk ICU pts (202)	53	64
		IAC or urologic candidiasis (11) vs at-risk ICU pts and healthy controls (76)	73	54
		IAC (18) vs at-risk ICU pts (18)	61	80

CJ Clancy & MH Nguyen. J Clin Microbiol. 2018; 56: e01909.

Performance of nonculture tests for diagnosing intra-abdominal candidiasis

Test	Method	Study groups (*n*)	Sensitivity (%)	Specificity (%)
1,3-β-^{D}-glucan	Fungitell	IAC (34) vs at-risk ICU pts (73)	56	73
		IAC (29) vs at-risk ICU pts (60)	65	78
		AC or urologic candidiasis (11) vs at-risk ICU pts and healthy controls (76)	64	83
		IAC (20) vs at-risk ICU pts (202)	77	57

CJ Clancy & MH Nguyen. J Clin Microbiol. 2018; 56: e01909.

Performance of nonculture tests for diagnosing intra-abdominal candidiasis

Test	Method	Study groups (*n*)	Sensitivity (%)	Specificity (%)
PCR	*Candida* real-time PCR panel	IAC (34) vs at-risk ICU pts (73)	88	70
	Multiplex *Candida* real-time PCR	IAC or urologic candidiasis (11) vs at-risk ICU pts and healthy controls (76)	91	97
		IAC (20) vs at-risk ICU pts (202)	86	33

CJ Clancy & MH Nguyen. J Clin Microbiol. 2018; 56: e01909.

Interpreting nonculture test results

- No matter how sensitive or specific a nonculture assay may be, clinicians must accept a level of uncertainty when interpreting results.
- Positive predictive values and negative predictive values are dependent upon sensitivity, specificity, and the pretest likelihood of invasive candidiasis.

CJ Clancy & MH Nguyen. J Clin Microbiol. 2018; 56: e01909.

Interpreting nonculture test results

- Pretest likelihoods of candidemia and intra-abdominal candidiasis can be estimated from disease prevalence in various clinical settings.
- In most settings, positive predictive values of nonculture test are low, and negative predictive values are high.
- For tests to be useful, clinicians must understand the pretest likelihood of invasive candidiasis and test performance for the most common disease manifestation in a given patient.

CJ Clancy & MH Nguyen. J Clin Microbiol. 2018; 56: e01909.

Early recognition

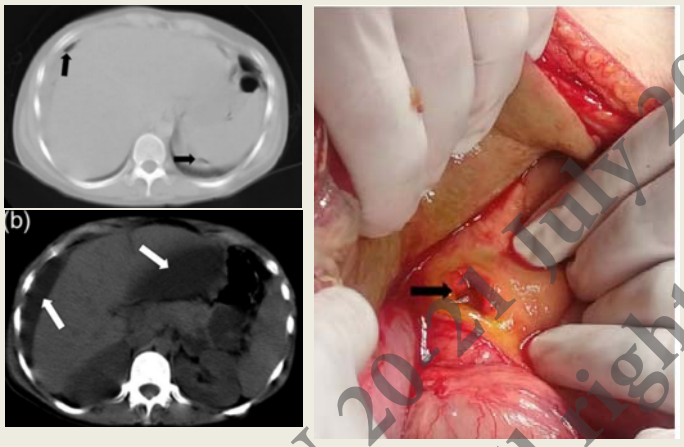
- The occurrence of *Candida* superinfection in patients with prior sepsis/bacterial infection
  - Blunted immune response
  - Polymicrobial infection
- The presence of intra-abdominal pathological change:
  - hollow visceral perforation
  - presence or recurrence of tumors

The role of inflammatory biomarkers

- C-reactive protein
- Procalcitonin
  - Most studies did show lower PCT values in patients with candidemia compared to bacteremia
  - None of the studies retrieved actually studied guidance of antifungal treatment by PCT.
  - PCT may improve diagnostic performance regarding candidemia when combined with other biomarkers of infection (e.g., beta-D-glucan) but more data is needed.

Andrea Cortegiani, et al. Crit Care. 2019; 23: 190.

Fungal peritonitis and high ascitic amylase as a rare manifestation of gastric perforation



Lugien Alasadi, et al. Oxf Med Case Reports. 2019; 2019: omz022.

Early Source Control and Antifungal Treatment

- C. *albicans* (56%) and C. *glabrata* (24%) were the most common species.
- Bacterial co-infections and candidemia occurred in 67% and 6% of patients, respectively.
- 72% of patients underwent an early source control intervention (within 5 days) and 72% received early antifungal treatment.
- 100-day mortality was 28%, and highest with primary (88%) or secondary (40%) peritonitis. Younger age, abscesses and early source control were independent predictors of survival.
- Infectious diseases consultations were obtained in only 48% of patients. Consulted patients were significantly more likely to receive antifungal treatment.

PloS One 2016; 11(4): e0153247.

Recommendations on the management of intra-abdominal candidiasis

- Direct microscopy examination for yeast detection from purulent and necrotic intra-abdominal specimens during surgery or by percutaneous aspiration is recommended in all patients with nonappendicular abdominal infections including secondary and tertiary peritonitis.
- Prophylactic usage of fluconazole should be adopted in patients with recent abdominal surgery and recurrent gastrointestinal perforation or anastomotic leakage.
- Empirical antifungal treatment with echinocandins or lipid formulations of amphotericin B should be strongly considered in critically ill patients or those with previous exposure to azoles and suspected intra-abdominal infection with at least one specific risk factor for *Candida* infection.

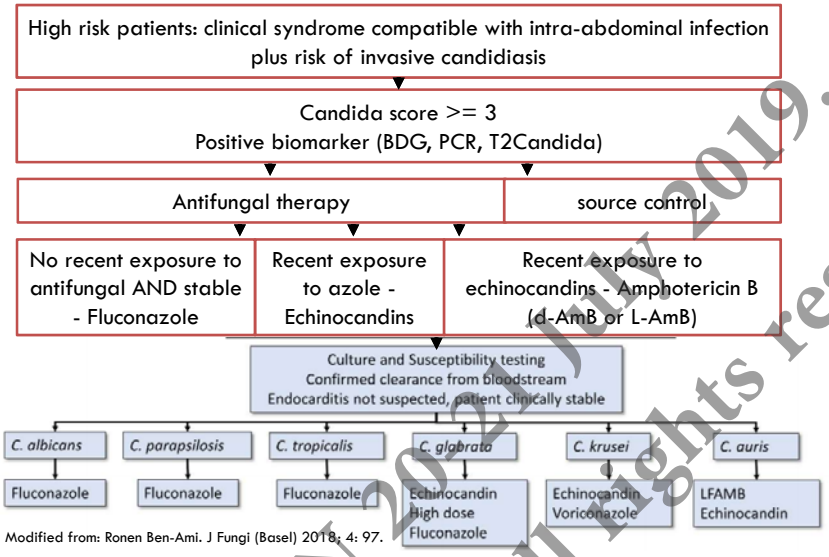
Bassetti M, et al. Intensive Care Med. 2013;39:2092

Recommendations on the management of intra-abdominal candidiasis (cont.)

- In patients with nonspecific risk factors, a positive mannan/antimannan or (1→3)-β-D-glucan or polymerase chain reaction test result should be present to start empirical therapy.
- Fluconazole can be adopted for the empirical and targeted therapy of non-critically ill patients without previous exposure to azoles unless they are known to be colonized with a *Candida* strain with reduced susceptibility to azoles.
- Treatment can be simplified by stepping down to an azole (fluconazole or voriconazole) after at least 5-7 days of treatment with echinocandins or lipid formulations of amphotericin B, if the species is susceptible and the patient has clinically improved.

Bassetti M, et al. Intensive Care Med. 2013;39:2092

Treatment algorithm for patients with suspected or confirmed intra-abdominal candidiasis



Modified from: Ronen Ben-Ami. J Fungi (Basel) 2018; 4: 97.

Conclusion

- *Candida* species are a part of the human microbiome and can cause intra-abdominal candidiasis in patients with impaired systemic or local immunity.
- Intra-abdominal candidiasis consists a diversity of diseases and is associated with heterogeneous manifestations, which may result in poor outcomes.
- It highlights the importance of careful clinical evaluation and a multi-disciplines approach in high risk patients
  - *Candida* isolated from abdominal drains or samples collected during operation plus biomarkers
  - Identify and control the source
  - Antifungal treatment
  - The role of infectious disease physicians